PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 964-104PCT	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/CA 03/00847	International filing date *(day/month/year)* 11.06.2003	Priority date *(day/month/year)* 11.06.2002
International Patent Classification (IPC) or both national classification and IPC A61K31/56		
Applicant PANAGIN PHARMACEUTICALS INC. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 7 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
09.01.2004	13.09.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Bochelen, D Telephone No. +49 89 2399-8150

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA 03/00847

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

3-34	as originally filed
1, 2	filed with telefax on 17.08.2004

Claims, Numbers

1-30	filed with telefax on 17.08.2004

Drawings, Sheets

1/6-5/6	as originally filed
6/6	filed with telefax on 17.08.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

   see separate sheet

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 21-28

   because:

   ☒ the said international application, or the said claims Nos. 21-28 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/ or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-30
	No:	Claims	
Inventive step (IS)	Yes:	Claims	3-6
	No:	Claims	1-2,7-30
Industrial applicability (IA)	Yes:	Claims	1-20,29-30
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item I
Basis of the report

1. The amendments filed with the telefax dated 17.08.2004 introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 34(2)(b) PCT. The amendments concerned are the following:

   the feature "enhanced anti-cancer activity" has no basis in the application as filed.

   new figure 5 has no basis in the application as filed. The brief description of the figure 5 on page 31 does provide basis for the new figure 5. It is noted that it is not allowable to introduce new data from priority document in the application.

Re Item III
Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

2. Claims 21-28 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V
Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D2: PATENT ABSTRACTS OF JAPAN vol. 007, no. 242 (C-192), 27 October 1983 (1983-10-27) & JP 58 131999 A (OOSAKA YAKUHIN KENKYUSHO:KK;OTHERS: 01), 6 August 1983 (1983-08-06)
D3: FR-A-2 430 234 (ARICHI SHIGERU) 1 February 1980 (1980-02-01)
D4: PATENT ABSTRACTS OF JAPAN vol. 004, no. 190 (C-037), 26 December 1980 (1980-12-26) & JP 55 129228 A (OSAKA CHEM LAB), 6 October 1980 (1980-10-06)
D5: WO 01/82908 A (UNIV BRITISH COLUMBIA ;JIA WILLIAM (CA)) 8 November 2001 (2001-11-08)
D6: KIM ET AL: "GINESONIDE RH-2 INDUCES APOPTOTIC CELL DEATH IN

RAT C6 GLIOMA VIA A REACRTIVE OXYGEN- AND CASPASE-DEPENDENT BUT BCL-XL-INDEPENDENT PATHWAY" LIFE SCIENCES, vol. 65, no. 3, 1999, pages PL33-PL40, XP002255323

D7: SHIBATA S: "CHEMISTRY AND CANCER PREVENTING ACTIVITIES OF GINSENG SAPONINS AND SOME RELATED TRITERPENOID COMPOUNDS" JOURNAL OF KOREAN MEDICAL SCIENCE, KOREAN ACADEMY OF MEDICAL SCIENCE, SEOUL, KR, vol. 16, no. SUPPL, December 2001 (2001-12), pages S28-S37, XP001164163 ISSN: 1011-8934

2. Prior art:

Document D2 discloses the antitumour activity of the sapogenins protopanaxadiol and protopanaxatriol extracted from Panax ginseng.

Document D3 discloses compositions comprising several saponins extracted from plants of the genus Panax, e.g. Panax ginseng, Panax quinquefolium, Panax notoginseng, and the use thereof for treating cancer.

Document D4 discloses compositions comprising saponins extracted from Panax ginseng.

Document D5 discloses the use of the ginsenoside Rh2 for cancer in combination with paclitaxel and to increase the sensitivity of multidrug resistant cancer cells to paclitaxel or mitoxantrone.

Document D6 discloses the induction of apoptosis in glioma cells by the ginsenoside Rh2.

Document D7 discloses the inhibition of ovarian cancer cell tumours by ginsenoside Rh2. It is suggested that the active antitumour agent is the deglycosilated product protopanaxadiol.

If not indicated otherwise the relevant passages are those mentioned in the search report.

3. Novelty:

The subject-matter of the present claims 1, 13-14, 21 and 29-30 relates to the

combination of one or more saponins with one or more sapogenins and the use thereof in the anti-cancer therapy. The prior art does not disclose such a combination. Claims 1, 13-14, 21 and 29-30 fulfill the requirements of Art. 33(2) PCT.

4.Inventive step:

4.1 Document D3 which is considered to be the closest prior art discloses saponins, like Rg1, Rg2 or Rb1 (see p4 l31-39) for the treatment of cancer. The present claims differ in that saponins are combined with sapogenins. The problem to be solved may thus be regarded as to provide an improved anti-cancer agents. The application provides evidence for a synergistic effect only for the combination of Rh2, aglycon protopanaxotriol and aglycon protopanaxadiol (see figures 1-3). It is thus considered that the problem is not solved over the whole scope of the claims. The combination of any saponin with any sapogenins would be obvious in view of the prior art when combining D2 and D3. The subject-matter of claims 1, 13-14, 21 and 29-30 does thus not involve an inventive step in the sens of Art. 33(3) PCT.

4.2 Dependent claims 2, 7-12, 15-20, 22-28 do not appear to contain any additional feature which, in combination with the features of any claim to which they refer, meet the requirements of the EPC with respect to novelty and/or inventive step.

4.3 The combination of Rh2, aglycon protopanaxotriol and protopanaxadiol results in a synergistic anti-cancer activity (see figures 1-3). An inventive step is thus acknowledged for claims 3-6.

5. Industrial applicability:

For the assessment of the present claims 21-28 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

COMPOSITIONS FOR CANCER THERAPY SAPONINS OR SAPOGENINS

FIELD OF THE INVENTION

The present invention pertains to the field of cancer therapy and in particular to compositions comprising saponins and/or sapogenins for use in the treatment of cancer.

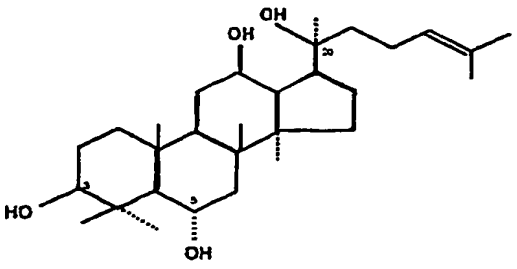
BACKGROUND

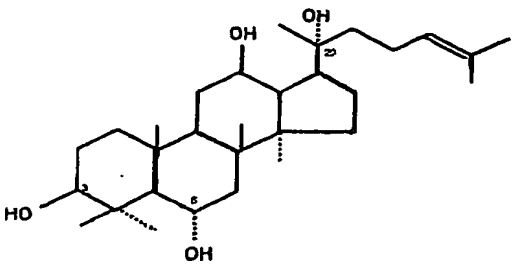
There is a continuing need for development of new anti-cancer drugs and drug combinations. Accordingly, cancer research has been increasingly directed to the discovery of novel anti-cancer agents obtained from natural sources, as well as identifying and preparing synthetic compounds found in these natural sources.

Ginseng has long been recognized as a general tonic and a benign and safe herb. Many of the components of ginseng have been isolated and have been classified as: ginsenosides, carbohydrates, nitrogenous compounds, fat-soluble compounds, vitamins and minerals. The saponins derived from ginseng (also called "ginsenosides") are believed to be the main active components of ginseng.

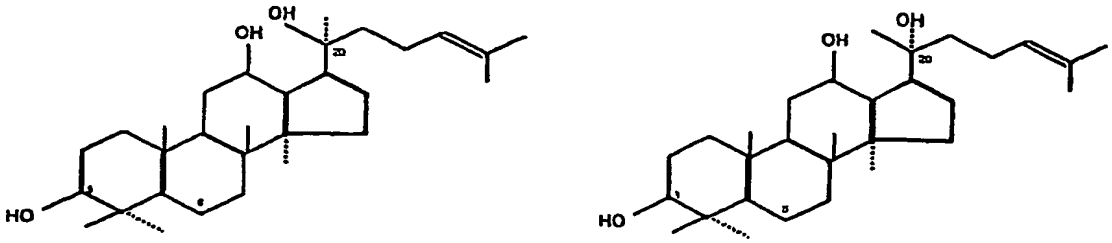
Saponins, in general, are composed of a sugar portion (glycon) and a non-sugar portion (aglycon or sapogenin). The sapogenins in ginseng, the backbone of saponins, are further classified into three types: protopanaxadiol and protopanaxatriol (which are tetracyclic terpenoids of the dammarane series), and oleanoic acid.

The sapogenin aglycon protopanaxatriol (aPPT) has the following chemical structures:



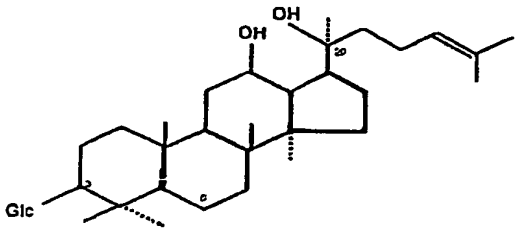


The sapogenin aglycon protopanaxadiol (aPPD) has the following chemical structure:



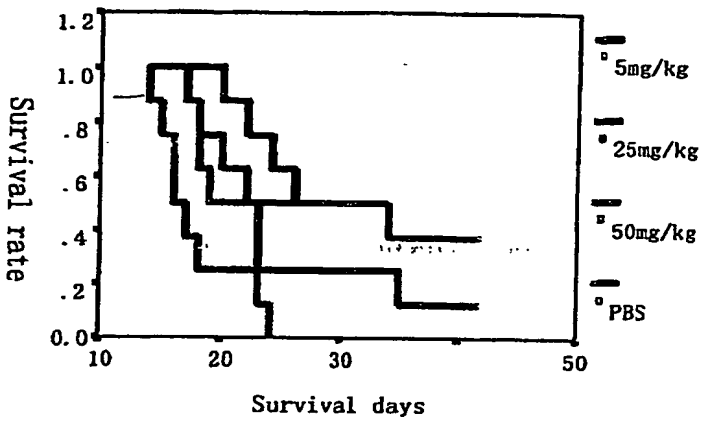
More than 25 dammarane-type saponins have been isolated from Panax ginseng C.A. Meyer, which vary in the number and type of monosaccharide residues present in the sugar side chains. The individual ginsenosides are named Rx according to their mobility on thin-layer chromatography plates. Examples of known ginsenosides include those in groups Ra through Rh. The isolation of three new dammarane-type saponins (named Rk1 to Rk3) from heat-processed ginseng has also been reported recently (see Park, I.H. (2002) Arch Pharm Res. 25: 428-32).

In recent years, the beneficial effects of ginsenosides in the treatment of cancer has been reported. For example, U.S. Patent Application Nos. 09/910,887 (published as: 20030087835) and 09/982,018 (published as: 20030087836) describe novel sapogenin compounds having anti-cancer activities. Similarly, U.S. Patent No. 5,776,460, reports ginsenoside Rh2 [3-O-β-D-glucopyranosyl-20(s)- protopanaxadiol] to have anti-cancer activities. Rh_2 is a saponin having the following chemical structure, in which "Glc" is the glycon (glucose):



The literature also shows that Rh2 can induce differentiation and apoptosis of cancer cells (Kikuchi Y. et al. (1991) Anti-cancer Drugs. 2: 63-7; Lee KY et al. (1996)

Figure 5: ***In vivo*** **cancer inhibitory effect of various concentrations of Composition #4.**



THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A composition comprising an activity-enhancing amount of one or more saponins in combination with one or more sapogenins, and having an enhanced anti-cancer activity.

2. The composition according to claim 1, wherein the saponins and sapogenins are selected from the group comprising: Rh2, Rg3, aglycon protopanaxatriol, and aglycon protopanaxadiol.

3. The composition according to claim 2, comprising about 70% sapogenins, about 8% Rh2, and about 2% Rg3.

4. The composition according to claim 2, comprising between about 1-90% each of Rh2, aglycon protopanaxatriol, and aglycon protopanaxadiol.

5. The composition according to claim 4, comprising between about 1-50% of Rh2, between about 5-40% of aglycon protopanaxatriol, and between about 5-75% of aglycon protopanaxadiol.

6. The composition according to claim 5, comprising between about 5-40% of Rh2, between about 5-40% of aglycon protopanaxatriol, and between about 10-70% of aglycon protopanaxadiol.

7. The composition according to any one of claims claims 1 to 6, wherein one or more of said saponins and sapogenins are extracted from plant material.

8. The composition according to claim 7, wherein said plant material is derived from one or more plant from the genus *Panax*.

9. The composition according to claim 8, wherein said plant is *Panax ginseng*.

10. The composition according to claim 8, wherein said plant is *Panax quinquefolium*.

11. The composition according to claim 8, wherein said plant is *Panax notoginseng*.

12. The composition according to any one of claims 1-11, wherein one or more of said saponins and sapogenins are synthetic.

13. A pharmaceutical formulation for the treatment of cancer, comprising a therapeutically effective amount of the composition according to any one of claims 1-12 and a pharmacologically acceptable carrier.

14. A non-pharmaceutical formulation for the treatment of cancer, comprising a therapeutically effective amount of the composition according to any one of claims 1-12 and a pharmacologically acceptable carrier.

15. The formulation according to claim 13 or 14, wherein the formulation is in an orally administrable form.

16. The formulation according to claim 13 or 14, wherein the formulation is in an injectable form.

17. The formulation according to claim 13 or 14, wherein the formulation is in a topically applicable form.

18. The formulation according to claim 13 or 14, wherein said therapeutically effective amount comprises a dosage of between 0.01 mg to 1000 mg of Rh2 per kg bodyweight per day.

19. The formulation according to claim 13 or 14, wherein said therapeutically effective amount comprises a dosage of between 0.01 mg to 1000 mg of aglycon protopanaxatriol per kg bodyweight per day.

20. The formulation according to claim 13 or 14, wherein said therapeutically effective amount comprises a dosage of between 0.01 mg to 1000 mg of aglycon protopanaxadiol per kg bodyweight per day.

21. Use of the composition according to any one of claims 1-12 for the treatment of cancer in a mammal.

22. The use according to claim 21, wherein said cancer is selected from the group consisting of glioma tumor, melanoma, breast cancer, pancreatic cancer, brain tumor, intestinal and gastric cancers, prostate cancer, and lung cancer.

23. The use according to claim 21, wherein said cancer is selected from the group consisting of stomach cancer, esophagus cancer, colon and rectum cancer, ovary cancer, liver cancer, kidney cancer, larynx cancer, bone cancer, multiple myeloma, bladder cancer, cancer in body of uterus, oral cavity cancer, thyroid cancer, cervix cancer, testis cancer, non-Hodgkin's lymphoma, leukemia, Hodgkin's disease, skin cancer, and soft tissue cancer.

24. The use according to claim 21, wherein said cancer is a multi-drug resistant cancer.

25. The use according to claim 24, wherein said multi-drug resistant cancer is a primary cancer selected from the group consisting of cancers of muscle, bone or connective tissues, the skin, brain, lungs, sex organs, the lymphatic or renal systems, mammary or blood cells, liver, the digestive tract, pancreas and thyroid or adrenal glands, including solid tumors, cancers of the ovary, breast, brain, prostate, colon, stomach, kidney or testicles, Kaposi's sarcoma, cholangioma, chorioma, neuroblastoma, Wilms' tumor, Hodgkin's disease, melanomas, multiple myelomas, lymphatic leukemias and acute or chronic granulocytic lymphomas.

26. The use according to claim 24, wherein said multi-drug resistant cancer is a recurrent cancer selected from the group consisting of pancreatic cancer, lung cancer, stomach cancer, esophagus cancer, colon and rectum cancer, brain cancer, ovary cancer, liver cancer, kidney cancer, larynx cancer, bone cancer, multiple myeloma, melanoma, breast cancer, prostate cancer, bladder cancer, cancer in body of uterus, oral cavity cancer, thyroid cancer, cervix cancer, testis cancer, non-Hodgkin's lymphoma, leukemia, Hodgkin's disease, skin cancer, and soft tissue cancer.

27. The use according to any one of claims 21-26, wherein said composition is used in combination with one or more other chemotherapeutic agents.

28. The use according to any one of claims 21-26, wherein said mammal is a human.

29. The use of a composition according to any one of claims 1-12 in the manufacture of a medicament for the treatment of cancer.

30. A pharmaceutical kit for the treatment of cancer in a mammal comprising the composition according to any one of claims 1-12 and one or more containers.